DETAILED ACTION

Please note: the examiner of record has changed. Please address all future correspondence to the examiner listed at the conclusion of this action, Shannon Janssen.

Claim Status

1. Claims 4-12, 14 and 23-26 have been cancelled.

Claims 1-3, 13, and 15-22 are currently pending.

Claims 1-3, 13 and 15-22 are being examined in this application.

Election/Restrictions

2. Applicant's election without traverse of Group I (Claims 1-22) in the reply filed on 10/18/06 is as previously acknowledged.

3. Applicant's election without traverse of the following species:

A.) nucleic acids for the biopolymers;

B.) fluorescent groups, specifically, stilbene, as the detectable protecting groups;

C.) Compound (f) in Figure 5 as the core structure;

in the reply filed on 10/18/06 and 3/6/07 is as previously acknowledged.

Priority

4. This application claims foreign priority to EPO 03006098.2 (3/19/03).

5. Receipt is as previously acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Withdrawn Rejections

The rejection of Claims 1-3, 12, 13 and 15-22 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the claim amendments received December 18, 2009.

New Claim Objection(s)

Claim 2 is objected to because of the following informalities: Claim 2 recites "selected from the group consisting of compounds comprising....or coumarin", which is improper Markush format. Claim 2 should read "selected from the group consisting of compounds comprising....and coumarin". Appropriate correction is required.

Maintained Rejections

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

McGall and Others

8. Claims 1-3, 13 and 15-22 are rejected under **35 U.S.C. 103(a)** as being unpatentable over **McGall** et al (US 6,238,862; 05/29/2001), **Wagner** et al (Helvetic Chimica Acta. Vol. 80: 200-212. 1997; cited in IDS filed on 9/22/04), in view of **Hobbs** et al (5,151,507; 9/29/1992; cited previously), **Chen** et al (Journal of Organic Chemistry. Vol. 66: 1725-1732; 2001; cited previously) and **Agris** (PGPUB 20020045167; 4/18/2002; cited previously). The previous rejection is maintained for the reasons of record as set forth in the previous Office action as well as for the reasons below. Modifications to the rejection were necessitated by the claim amendments received December 18, 2009.

The instant claims recite a "quality control method for achieving complete deprotection of protected reactive groups in on-chip synthesis of a biopolymer array, the method comprising

(a) synthesizing a plurality of different biopolymer species on an array from monomeric or oligomeric building blocks comprising detectable protecting groups coupled directly to amino groups of the nucleotide building blocks and the detectable protecting groups remain coupled until synthesis of the biopolymer array,

(b) taking one or more steps to cleave the detectable protecting groups,

(c) determining a degree of deprotection by detecting detectable protecting groups remaining on the array after cleavage, and

(d) repeating steps (b) and (c) until detectable protecting groups are no longer detected, indicating that complete deprotection is achieved, wherein the quality control method is performed entirely on-chip."

McGall et al, throughout the patent, teach methods of quality control for manufacturing nucleic acid probe arrays (e.g. Abstract and Claim 1 of the reference), which reads on the quality control method of **clm 1**.

The reference teaches synthesizing nucleic acids using protected monomers such as 5' and 3' protected nucleotides (e.g. Claims 5, 12 and 23; col. 2, lines 40+; Figures 9-10; col.4, lines 51+), which reads on synthesizing biopolymer on an array using protected nucleic acid monomers of step (a) of **clm 1**.

The reference teaches "deprotecting" (or removal) of the protecting group at the end of each round of synthesis and "deprotecting" (or cleaving) the side chain protecting groups at the conclusion of the array synthesis (e.g. Claim 23; col. 2, lines 40+, col 5, lines 5-10; Figure 9), which reads on the cleaving the protecting group of step (a) of **clm 1**. The reference teaches, for example, "photolabile groups" (i.e. protection groups) and "side chain protective groups" are removed after the desired products are produced (i.e. the desired product would be the complete oligonucleotide array; e.g. col.5, lines 2), which reads on the step of cleaving the protecting groups as recited in step (b) of **clm 1**. In addition, the reference teaches that the oligonucleotides are not "consumed" or "eliminated" by the process, in the sense that they remain on the array (e.g. col 5 and 14).

The reference teaches "determining the amount of unprotected active sites" (col. 2, lines 49+) by detecting the amount "detectable labels" on the array (col. 2, lines 40+; cols. 8-9; Figure 7; especially, col.9, lines 9+), which reads on step (c) of **clm 1**.

The reference also teaches repeating steps of "deprotection" (e.g. claim 12), which reads on the repeated deprotection step (step (d)) of **clm 1**.

The reference teaches the detectable label (or protecting label) is a fluorescent label such as a rhodamine (e.g. Claims 26 and 27 of the reference), which reads on the "fluorescent groups" of **clm 2** and rhodamine of **clm 3**.

The reference teaches the fluorescent label is linked (or coupled) to the nucleotide (e.g. Figure 6). The reference teaches linking the fluorescent label through the phosphate group in the sugar group of the nucleotide (e.g. Figure 6).

McGall et al do not explicitly teach the protection groups are directly coupled to and protect the nucleobase amino groups as recited in the amended **clms 1** and **13**. The reference also does not explicitly teach the repeating steps of deprotection and detection (until "completion") as recited in the amended **clm 1**. The reference also does not teach using "stilbene" (the elected species) as the "fluorescent group", as recited in **clm 3**. The reference also does not explicitly teach the various chemistries recited in **clms 15-22**.

However, McGall et al., teach repeating steps of "deprotection" (e.g. claim 12). It would have been prima facie obvious for one of ordinary skill in the art to repeat both the deprotection and detection steps for the desired results measuring deprotection at different stages. It would have been obvious to one of ordinary skill in the art to apply the standard technique of repeating deprotection and detection steps as the procedure for performing the said steps are taught by McGall, to improve the deprotection (such as to render various degrees of deprotection) and detection (such as to generate an average measurements) for the predicable result of enabling standard oligonucleotide synthesis and the accompanying quality control measurements.

Wagner et al, throughout the publication, teach methods of nucleic acid synthesis using protected nucleotides. (see Abstract). The reference teaches synthesis of various oligonucleotides

using protected nucleotides (pp. 204-206; especially Table 1 and p. 204, last para). The reference teaches the fluorescent label is linked directly to the amino group of the nucleobases (e.g. p. 202, Schemes 1-2), which reads on the "coupled to nucleobases" of **clm 13**, and coupling through the amino groups of **clm 1**. The reference also teaches detecting the protecting groups attached to the synthesized oligonucleotides (e.g. pp.206-207). The reference also teaches deprotecting the label attached nucleobase after the synthesis of the oligonucleotide (e.g. pp.205-206; Figure on pg.206).

The reference teaches the detectable label (or protecting label) is a fluorescent label such as a "dnseoc" (or a "dansyl") (e.g. p. 201, para 3 and Figures), which reads on the "fluorescent groups" of **clm 2** and "dansyl" of **clm 3**. The "dnseoc" ((dansylethoxy)carbonyl) group also reads on the "L" group when n=1 (as recited in **clm 21**), because the carbonyl group reads on the formula "C(O)" and the dansyl group reads on formula "R".

The reference also teaches the structure of nucleotides comprising a base (protected by dnseoc), a sugar, a protected hydroxyl group, and a protected phosphate group (e.g. Scheme 2, Scheme 5). The $(MeO)_2TrO$ (or Dimethoxytrityl) group in Scheme 5 of the reference (see p. 201, para 4 and p. 204) reads on the hydroxyl protection group, DMTrO (the elected species of ; see Reply, filed 3/6/07, p. 2) or the "triphenylmethyl" group of **clms 15**, **16,** and **17**.

The reference also teaches phosphate protection group such as the "(2-cyanoethoxy)bis(diisopropylamino)phosphine" at the 3' sugar position (p. 204, para 1 and Scheme 5), which is the same phosphoramidite (phosphate amide) (i.e. the R3, R4, R5 and R6 groups of compound (f) in Figure 5 (the instant elected species; Reply, filed 3/6/07)), as recited in **clms 18**, **19**, and **20**.

The reference also teaches various nucleobases such as C, A, and G (e.g. p. 204, Scheme 5), which read on the nucleotide bases recited in **clm 22** and the elected species of adenine.

Agris, teaches methods of monitoring the degree of deprotection "after" synthesis of oligonucleotides on arrays by detecting detectable protecting groups "on the array" (e.g. Abstract; claims 14-18, 45 and 51; p.9, [0158]+) and that the detection can be repeated to detect a plurality of protecting groups (e.g. [0162]). The reference also teaches the protecting group is attached to the nucleotide base through the amino group of the base (e.g. p.5, [0046]+). The reference also teaches the need for such detection so that simple and reliable techniques for determining the purity of the desired oligoncleotides can be carried out (e.g. p.1, [0005]). In addition, the reference teaches that the oligonucleotides are not "consumed" or "eliminated" by the process, in the sense that they remain on the array (e.g.: [0164-0166]).

Hobbs et al teach using various fluorescent molecules to label (or protect) nucleotides (see Abstract). The reference teaches "stilbene" can be used to attach to the nucleobases (col. 30, lines 20+) through linkers that comprise "carbonyl" group (reads on the formula of "COR" of **clm 21**; col. 11, lines 50+). The reference also teaches various fluorescent dyes can be used depending on the different applications (cols. 12+).

In addition, **Chen et al**, teaches attaching "stilbene" to nucleosides (see Abstract). The Chen reference also teaches "stilbene" has "bright fluorescence of very high quantum yield" (p. 1725, right col., para 2).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to attach a fluorescent group such as "stilbene" to a "monomeric

building block" (such as a nucleoside) to the amino groups of the nucleobase for various assays such as detecting the attached fluorescent group on an oligonucleotide array.

A person of ordinary skill in the art would have been motivated at the time of the invention to couple the protection group to the amino group of the nucleobase, because the nucleobase protection groups offer the advantages of providing more efficient and fast working oligodeoxyribonucleotide synthesis, as taught by Wagner et al (e.g. p.200). In addition, because both the McGall reference and the Wagner reference teach methods of using protected monomers (nucleotide building blocks) to generate oligonucleotides with detection of the degree of deprotection (for either the sugar phosphate groups or the nucleobase groups) that are necessary for completion of oligonucleotide synthesis, it would have been obvious to one skilled in the art to substitute one detection method of detecting the deprotection of the sugar phosphate reactive groups for the other (the deprotection of the nucleobase groups) to achieve the predictable result of determining the degree of deprotection for a solid state oligonucleotide synthesis. In addition, the Agris reference teaches detecting the degree of deprotection (from the amino groups) after oligonucleotide array synthesis by measuring the amount of the protecting groups "remaining on the array" (i.e. on-chip analysis), as discussed supra. The Agris reference also teaches the need for such on-chip detection so that simple and reliable techniques for determining the purity of the desired oligonucleotides on an array can be achieved. Thus, it would have been obvious to one skilled in the art to substitute one detection method (such as using antibody recognition on the array) for the other (fluorescence detection on the array) to achieve the predictable result of detecting the protecting group remaining attached to the nucleotide bases on the synthesized oligomer array to improve the quality control method for array synthesis.

A person of ordinary skill in the art would also have been motivated at the time of the invention to directly detect the remaining detectable protecting group on an array to assess the purity of the synthesized oligonucleotides, because Agris teaches the need for such as a simple and reliable technique to control the quality of the synthesized microarray, as discussed supra. In addition, it would have been prima facie obvious for a person of ordinary skill in the art to use fluorescent groups (such as stilbene) as the protecting group and to measure the remaining fluorescent signals after cleavage to assess the degree of protection, to improve the quality control assay for the deprotection step during an array generation (of methods such as McGall et al) for the predictable result of enabling routine oligonucleotide synthesis on an array with various known protection and labeling groups.

A person of ordinary skill in the art would have been motivated at the time of the invention to use "stilbene" as the "detectable protecting group", because "stilbene" is a known fluorescent label for biomolecules (especially nucleotides), and stilbene is known to exhibit "bright blue fluorescence of very high quantum yield", as taught by both Hobbs et al and Chen et al.

A person of ordinary skill in the art would have been motivated at the time of the invention to use the specific nucleotide building blocks and their corresponding chemistry to generate the required reagent for the method of detecting deprotection, because the structures for basic nucleotide building blocks are known in the art, and the various protection groups are known and routine in the art as taught by Wagner et al. In addition, Wagner et al also teach the advantages of using these nucleotide building blocks and their corresponding protection groups,

including providing efficient and fast working oligonucleotide synthesis as well as fast and effective cleavage of the protection group (e.g. pp.200-201).

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since McGall et al, Wagner et al, Hobbs et al and Chen et al have demonstrated successful attachment of various protection groups such as fluorescent groups (especially stilbene) to nucleosides through known reaction mechanisms (such as the formation of -HN-C=O linkage between the nucleobases and the stilbene molecule) as well as using various nucleotide building blocks to build oligonucleotides, as demonstrated by the said references.

Discussion and Answer to Argument

9. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants' arguments are addressed with the following discussion as well as the above modified rejection (in light of applicant's amendment to the claims).

In general, applicants traversed the above rejection over a combination of references by attacking each reference alone. (Reply, pp.7+).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants question how the "McGall" reference "can serve as the primary reference for finding "obviousness" of the instant claims" (Reply, p.8, para 1).

The McGall reference is relied on for the "quality control" of on-chip synthesis. The on-chip quality control method taught by McGall, the protecting groups taught by Wagner, and the on-chip quality control method for detecting remaining side chain protecting groups taught by Agris, and the other references, as a whole, is what obviates the instant invention.

Applicants argue the Wagner reference does not teach "on-chip quality control assessment of deprotection of the amine side chains" (Reply, p.8, para 2+).

However, the above rejection is not over the Wagner reference alone. Applicants are respectfully directed to the above rejection for detailed discussion how the combination of the reference teaches all elements of the instant claims. The alleged deficiency of the Wagner reference is remedied by the above cited additional references (especially the Agris and McGall references).

Applicants assert there is no way to combine the methods, and no motivation to import elements from the teachings of Agris and Wagner into McGall (Reply, p.8, para 3).

However, the motivation to combine and methods to combine are discussed in detail; applicants are respectfully directed to the above modified rejection for the reasons to combine the cited references and how the combination of the cited references teaches all the elements.

Applicants assert the combination of references is based upon improper hindsight reasoning (Reply, p.8, para 3, p.9, para 3, p.10+).

In response, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, the methods of quality control as taught by the McGall reference, the different protective groups taught by the Wagner, Chen, and Hobbs references, and the need and methods for on-chip quality control for side chain deprotection as taught by the Agris reference were all well known to one of ordinary skill in the art.

Applicants assert that the Agris method reduces yield (Reply, p.9, para 2, p.11, para 2).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., that there is no reduction of yield) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicants assert that the Agris reference fails to teach additional cleavage reactions (Reply, p.9, para 2).

However, the above rejection is not over the Agris reference alone. Applicants are respectfully directed to the above rejection for detailed discussion how the combination of the reference teaches all elements of the instant claims. The alleged deficiency of the Agris reference is remedied by the above cited additional references (especially the McGall reference).

Applicants argue there is no motivation to combine McGall with Agris or Wagner (Reply, p.9, para 3+, p.10+).

In response, the examiner recognizes that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007). In this case, both the McGall reference and the Agris reference are drawn to quality control in oligonucleotide array synthesis. The fact that the McGall reference is primarily concerned with deprotection of the hydroxy group does not invalidate it as a reference for teaching on-chip quality control in oligonucleotide sythesis. As discussed supra, the Wagner reference teaches improved deprotection of side chains using the dnscoc groups, the Agris reference teaches the need for improved deprotection of side chains and quality control in array synthesis and methods of conducting quality control, and the McGall reference teaches methods of quality control in array synthesis. Applicants are respectfully directed to the above modified rejection for the reasons to

combine the cited references and how the combination of the cited references teaches all the elements.

Applicants argue the examiner argue independent motivations and combinations for each step of claim 1 (Reply, p.10, para 2).

The examiner has merely written the claim rejections for purposes of clarity. The summary following the detailed rejection of the claims explains the motivations and methods of combining the different references.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Future Communications

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHANNON JANSSEN whose telephone number is (571)270-1303. The examiner can normally be reached on Monday-Friday 9:00AM-6:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Amber D. Steele/
Primary Examiner, Art Unit 1639

Shannon L Janssen

SLJ